

# Optimizing reproductive health in women with obesity and infertility

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Infertility, defined as a failure to achieve a pregnancy after at least 12 months of regular and unprotected sexual intercourse, affects 15% of all couples in Canada.<sup>1</sup> Costs associated with assisted reproductive technologies are growing, such that equitable access to high-quality reproductive care is a challenge for health care systems. Obesity is a known modifiable risk factor for female infertility and can affect maternal health; it also puts the offspring's health at risk both as a newborn and later in life (cardiometabolic health).<sup>2</sup> As such, addressing obesity in women seeking to become pregnant would be prudent, especially given that 25% of Canadian women of reproductive age are overweight (body mass index [BMI] 25–30) and 19% are obese (BMI > 30).<sup>3</sup> We review evidence on the effects of obesity on women's fertility, recommendations regarding obesity management in women with infertility, and evidence of the benefits of weight loss and lifestyle changes for fertility and pregnancy outcomes (Box 1 outlines our search strategy).

## What is the relation between obesity and women's fertility?

The risk of infertility is increased by 78% and 27% in women of childbearing age with obesity and overweight, respectively, as compared with women of normal weight (BMI 18.5–25).<sup>4</sup> Obesity can negatively affect women's fertility via menstrual and ovulatory disorders. Such disorders include polycystic ovary syndrome (PCOS), the most common cause of female infertility, affecting 6% to 10% of women of child-bearing age. Insulin resistance is considered to play an important role in the association between PCOS and obesity, because elevated circulating levels of insulin stimulate androgen production by the ovaries.<sup>5</sup> Moreover, higher levels of circulating triglycerides and fatty acids, which are associated with obesity and insulin resistance, may directly induce androgen production in predisposed women.<sup>6</sup> Obesity, especially central obesity, exacerbates clinical features of PCOS:<sup>7,8</sup> obesity has a negative impact on the effectiveness of fertility treatments and confers a higher risk of pregnancy complications<sup>7</sup> and cardiometabolic diseases.<sup>5</sup> However, the negative effects of obesity on women's reproductive health are observed even in women with no apparent ovulatory or menstrual dysfunctions. In a large prospective cohort, with more than 3000 eumenorrheic

## KEY POINTS

- Obesity is a known risk factor for female infertility and can affect maternal and newborn health.
- Expert guidance recommends that women with obesity and infertility adopt a healthy lifestyle aimed at losing weight before natural or medically assisted conception.
- Lifestyle interventions promoting weight loss have, in most studies, shown improvement of fertility in women with obesity, mainly increasing the chance of spontaneous pregnancy.
- Lifestyle modification is the preferred approach to preconception weight loss, over bariatric surgery or pharmacologic agents.

women, there was a linear decline of 4% in the chances of a spontaneous pregnancy for each increase of one point in the BMI score in obese women.<sup>9</sup> Yet there are few existing cohort studies including obese women without PCOS, since the condition is fairly common, clinically exacerbated by obesity and the most common cause of infertility in women.<sup>10,11</sup>

In women seeking fertility treatments, obesity was associated with a decrease in pregnancy<sup>12,13</sup> and live-birth rates.<sup>13</sup> Furthermore, to achieve a pregnancy, women with obesity undergoing fertility treatments (intrauterine insemination or in vitro fertilization) are more likely to need higher doses of gonadotropin and have more cancelled cycles<sup>12,14</sup> and lower embryo quality.<sup>15</sup> A meta-analysis found no associations between being overweight and risks of ovarian hyperstimulation syndrome and multiple pregnancies compared with normal-weight women, but reported a slight decline in the live-birth rate following assisted reproductive technologies in obese women (odds ratio [OR] 0.90, 95% confidence interval [CI] 0.82–1.00).<sup>11</sup>

## What is the effect of maternal obesity at conception on offspring?

Although fertility treatments are becoming more efficient in overcoming the effects of obesity on women's fertility, prepregnancy and gestational obesity are serious risk factors for pregnancy and neonatal complications. According to an extensive systematic review of published reviews, pregnant women with

### Box 1: Evidence used in this review

We searched PubMed to find relevant reviews on the subject published within the past 10 years. We used a small number of keywords to broaden our research, mainly to reach all types of studies and interventions in obesity and fertility: ["weight loss" OR "weight management"] AND ["lifestyle" OR "multidisciplinary intervention/program"] AND ["fertil\*" OR "infertil\*" OR "pregnan\*"]. The search for these keywords was limited to titles and abstracts. Corresponding to our criteria, a total of 78 reviews were proposed, of which we included the 6 most recent and relevant to the subject. We added 14 original research articles because they were considered milestone studies in their field. Ten articles representing guidelines from health organizations relevant to the subject were also included in this review.

obesity have significantly higher odds of gestational diabetes (OR 3.01 to 5.55), preeclampsia (OR 2.93 to 4.14), antenatal (OR 1.43) and postpartum depression (OR 1.30), and cesarean delivery (OR 2.01 to 2.26), compared with normal-weight women.<sup>2</sup> Newborns born to mothers with obesity are at a higher risk of preterm birth (< 32 weeks' gestation; adjusted OR 1.33, 95% CI 1.12–1.57), macrosomia (> 4500 g; OR 3.23, 95% CI 2.39–4.37), perinatal death (relative risk 1.34, 95% CI 1.22–1.47) and congenital anomalies — including neural tube defects (OR 2.24, 95% CI 1.86–2.29) and cardiovascular anomalies (OR 1.30, 95% CI 1.12–1.51) — compared with newborns born to mothers with normal prepregnancy weight.<sup>2,16</sup> In addition, maternal prepregnancy BMI and excessive gestational weight gain are consistently associated with early development of obesity and diabetes in the offspring.<sup>17</sup> This risk may be carried through epigenetic mechanisms and perpetuates the transgenerational vicious cycle of obesity and cardiometabolic diseases.<sup>18</sup>

### How should physicians advise overweight and obese women who seek infertility treatment?

As outlined above, extensive data support strong associations between obesity and infertility in women, as well as notable pregnancy and neonatal complications for obese women. Accordingly, targeting women with obesity before conception may be essential to reduce the burden of infertility and costs of fertility treatment, as well as obesity and cardiometabolic diseases. As such, physicians should warn women with obesity seeking fertility treatments about the potential consequences on their own health and the health of their future child should they conceive. Many health organizations worldwide recommend that women with obesity be assisted to adopt a healthy lifestyle before conception and maintain it during pregnancy.<sup>19–23</sup> The 2007 consensus workshop group of the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine recommended a 5% decrease in body weight for women with PCOS who are obese as a first-line treatment.<sup>19</sup> Because the safety of hypocaloric diets, pharmacologic agents and bariatric surgery on pregnancy outcomes are not well understood, health care providers should advise women with obesity to improve their lifestyle before pre-

scribing any fertility treatments, according to guidance from expert bodies.<sup>20–22</sup> In 2010, the ESHRE pointed out that the goal of 5% weight loss should not be mandatory to access fertility treatments. However, lifestyle modifications before fertility treatments can improve success of the treatments, prevent pregnancy and neonatal complications, and limit associated costs.<sup>20</sup>

### Do lifestyle modifications and weight loss improve fertility outcomes in women with obesity and infertility?

Weight loss recommendations during the preconception period in women with obesity and infertility are primarily based on studies conducted in women with PCOS, among whom studies have shown that lifestyle modification can improve metabolic and reproductive outcomes.<sup>24</sup> Women with PCOS could benefit more from weight loss than women without PCOS because, for the same degree of obesity, they tend to have higher central obesity and insulin resistance,<sup>25</sup> which are linked to adverse metabolic and reproductive outcomes.<sup>5</sup> However, obesity and insulin resistance are important factors in the disturbance of the reproductive axis in women without PCOS as well.<sup>26</sup>

A systematic review of 11 observational studies and randomized controlled trials (RCTs), most of which included women undergoing in vitro fertilization treatments, found that the incidence of spontaneous pregnancy and live birth was increased in women allocated to a lifestyle intervention compared with controls.<sup>27</sup> Two three-arm RCTs involving women with obesity and PCOS who were previously resistant<sup>28</sup> or not<sup>29</sup> to clomiphene citrate reported that the combination of clomiphene citrate with lifestyle intervention increased the women's ovulation rates as compared with clomiphene citrate alone.

There are few studies that have assessed the benefits of lifestyle interventions as first-line therapy in the general population of women with obesity and infertility. An Australian research group reported in 1998 the fertility effects of a program that consisted of weekly group sessions with supervised physical activity practices and workshops covering different nutritional topics.<sup>30</sup> After 12 months of follow-up, 90% of women who completed the intervention resumed spontaneous ovulation, 78% conceived, of which 33% conceived spontaneously, and 67% delivered a live newborn, as compared with none of the women in the control group.

A recent multicentre RCT that enrolled more than 600 women evaluated a six-month lifestyle intervention designed to induce a 5% to 10% weight loss, before the initiation of assisted reproductive technologies.<sup>10</sup> In comparison to women having access to fertility treatments from the outset, and using intention-to-treat analyses, women in the experimental group displayed higher rates of spontaneous pregnancy (26.1% v. 16.2%; rate ratio 1.61, 95% CI 1.16–2.24) and needed fewer cycles of fertility treatment (679 v. 1067), albeit with a significantly lower rate of vaginal delivery of a live singleton after 24 months (27.1% v. 35.2%; rate ratio 0.77, 95% CI 0.60–0.99). Of note, the high drop-out rate of 22%, mainly observed in the intervention group, and the long follow-up duration may have diluted the true benefits of the intervention over time.

### Box 2: Unanswered questions

- By what mechanisms do lifestyle modification or weight loss improve reproductive function in women who are obese?
- Should weight loss, rather than lifestyle modifications, be the main focus in women who are obese and infertile?
- If weight loss is required in addition to lifestyle modification to improve fertility and pregnancy outcomes in women with obesity and infertility, what is the optimal weight-loss threshold that should be recommended?
- Do specific lifestyle modifications have a direct effect on fertility in addition to promoting weight loss?
- Are lifestyle interventions cost-effective in comparison to fertility treatments in women with obesity and infertility?
- In women with obesity, to what extent do preconception lifestyle modifications or weight loss prevent the risks of adverse maternal and neonatal outcomes, as well as the future development of cardiometabolic diseases in the offspring?

Evidence suggests that there is a dose–response relation between obesity and adverse reproductive effects in women,<sup>9,13</sup> but the optimal preconception weight loss and types of lifestyle interventions are not yet known, and further well-designed and sufficiently powered RCTs may offer a clearer evidence base.<sup>7</sup> Questions for future research are summarized in Box 2.

### Which interventions for weight loss should be considered for women with obesity who are trying to conceive?

Three main types of weight-loss interventions can be proposed to patients who are obese: modification of lifestyle habits, pharmacologic agents and bariatric surgery.

#### Bariatric surgery

According to a detailed systematic review on the long-term effect of weight-loss interventions in the general population, lifestyle interventions are less effective than bariatric surgery in terms of weight loss and risks of obesity-related comorbidities, such as type 2 diabetes.<sup>31</sup> However, the effects of weight loss through surgical interventions have not been thoroughly investigated in the context of infertility. Studies suggesting an improvement in spontaneous pregnancy rates after bariatric surgery are of low to moderate quality.<sup>32</sup> A recent retrospective cohort study assessed pregnant women after Roux-en-Y gastric bypass surgery compared with women matched for BMI who did not undergo surgery.<sup>33</sup> This study found a decrease in gestational hypertension and diabetes in the surgical group, but an increase in newborns small for gestational age. These results were confirmed in two recent reviews showing that bariatric surgery was associated with higher risk of newborns small for gestational age (OR 2.20, 95% CI 1.64–2.95) and a trend toward increased neonatal mortality (OR 2.39, 95% CI 0.98–5.85).<sup>34,35</sup> The American College of Obstetricians and Gynecologists states that surgical weight-loss interventions should not be considered as a fertility treatment and recommends delaying the time of conception to at least 12 to 24 months after the procedure.<sup>8,36</sup>

#### Pharmacologic agents

The safety of pharmacologic weight-loss agents approved for the treatment of obesity in pregnancy has not been sufficiently well studied to recommend their use in obese women with infertility.<sup>37</sup> Studies in this specific patient population may be warranted to understand their potential consequences on the health of mothers and their offspring.

Metformin has been extensively used in women with PCOS to improve their fertility, although it is not recommended as first-line therapy.<sup>38</sup> Its use has been associated with clinically significant and sustained weight loss in obese women with PCOS,<sup>39</sup> but because this effect is inconsistent and relatively mild, metformin is not considered a weight-loss therapy. Regarding its use during pregnancy, a double-blind RCT has reported that nondiabetic women taking metformin displayed lower gestational weight gain but had an increased risk of preeclampsia compared with a placebo.<sup>40</sup> No effects were observed on neonatal birth weight and risk of large-for-gestational-age newborns.<sup>40</sup>

#### Lifestyle interventions

Owing to the potential risks associated with bariatric surgery or weight-loss drugs, the only weight-loss intervention that health organizations recommend for women with obesity and infertility is support in adopting healthy lifestyle habits such as diet and physical activity.<sup>20,22,23,41</sup> According to the 2015 updated Canadian clinical practice guideline on the prevention and management of obesity in adults,<sup>42</sup> there is strong evidence supporting the importance of lifestyle interventions and programs in a multidisciplinary setting, including support from kinesiologists, dietitians and psychologists, to encourage and sustain weight loss. To promote healthy lifestyle and weight loss before conception in infertile women, our group<sup>43</sup> and others<sup>10</sup> have used a multidisciplinary approach including individual motivational interviews, advice on physical activity and counselling on nutritional habits. Physicians are encouraged to advise their patients on the importance of a healthy and balanced diet, as well as the regular practice of moderate to vigorous physical activities, aiming for 30 to 60 minutes daily. Motivational interviewing techniques should be used by physicians to help patients set SMART (specific, measurable, attainable, realistic, timely) objectives. Referrals of patients to dietitians and kinesiologists should be encouraged, when possible, to establish individualized diet and physical activity plans.

#### Conclusion

There is convincing evidence that obesity affects maternal, fetal and newborn health, as well as women's fertility. Evidence supports lifestyle modification and weight loss to improve fertility among women with obesity. Because of this evidence and the safety of lifestyle modification, women with obesity who seek fertility treatments should be well informed of these risks and encouraged to adopt a healthy lifestyle. Targeting women with obesity who consult fertility clinics and supporting them to engage in lifestyle changes before conception could reduce the burden of fertility-treatment costs, pre- and perinatal complications, and transgenerational transmission of cardiometabolic diseases.

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